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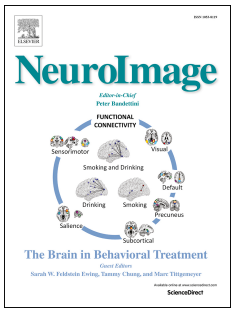

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Evidence for a functional specialization of ventral anterior temporal lobe for language

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Abstract

The controlled semantic cognition framework proposes that the ventral anterior temporal lobes (vATL) in the left and right hemisphere function as an integrated hub region supporting transmodal semantic representations. The clinical evidence for the transmodal function of vATL is largely based on studies of semantic dementia patients with severe anomia, who also show impaired performance on nonverbal tasks that involve the retrieval of knowledge about objects and their prototypical use, such as the production of tool use pantomimes. Yet, evidence from patients with apraxia and functional neuroimaging studies in healthy adults does not implicate vATL in pantomime production. We, therefore, compared semantic retrieval of object-action associations for overt verb and pantomime production from picture and word stimuli. Our results show that, independent of stimulus modality, the retrieval of object-action associations for verb, but not pantomime, production is related to activity in bilateral vATL. Bilateral vATL activation was also observed for meaningless verbal responses that did not require the retrieval of object-action associations. Taken together, our results suggest that bilateral vATL is not engaged in the retrieval of object-action associations per se, but rather supports semantic representations that are functionally specialized for language. These findings have implications for the semantic cognition framework and our understanding of the dependence of conceptual knowledge on language.

Keywords: verb; pantomime; semantic hub; nonverbal behaviour; tool use

Introduction

Semantic cognition constitutes an essential part of our ability to understand and interact with the world. The controlled semantic cognition framework proposes that semantic cognition relies on the interaction between two neurocognitive systems for conceptual representation and controlled retrieval (Patterson *et al.*, 2007; Lambon Ralph *et al.*, 2017). The framework further proposes that modality-specific conceptual representations are integrated in a transmodal, domain-general hub in the ventral anterior temporal lobe (vATL), which subserves the formation, maintenance, and retrieval of coherent, semantic associations across sensory and other modalities (Patterson *et al.*, 2007; Lambon Ralph *et al.*, 2017).

Some of the strongest evidence for a transmodal hub in the vATL comes from clinical studies investigating patients with the temporal variant of frontotemporal dementia, called semantic dementia, who have circumscribed atrophy in the vATL (Mummery *et al.*, 2000). The primary symptom of semantic dementia is severe anomia with preserved syntax, phonology, episodic memory, visual perception, and executive function (Snowden, Goulding, & Neary, 1989; Hodges *et al.*, 1992; Woolams *et al.*, 2008). Yet, despite being characterized by severe anomia, semantic dementia is classified as a memory disorder rather than a language disorder because a number of studies report that patients with semantic dementia also exhibit conceptual impairment on nonverbal tasks that require the retrieval of associations between objects and their typical use (Snowden, Goulding, & Neary, 1989; Hodges *et al.*, 2000; Bozeat *et al.*, 2002; Corbett *et al.*, 2009).

Together with functional neuroimaging studies, demonstrating that the vATL plays a role in a number of verbal and nonverbal semantic tasks in neurologically normal adults (Visser, Jefferies, Lambon Ralph, 2010; Rice *et al.*, 2015; Chen *et al.*, 2016), this clinical evidence suggests that verbal and non-verbal associations between objects and actions depend on a transmodal semantic hub in vATL. However, some evidence suggests that

semantic dementia is not necessarily associated with compromised conceptual knowledge of object use (Buxbaum, Schwartz, & Carew, 1997). In addition, clinical evidence from patients with post-stroke apraxia and functional neuroimaging studies in neurologically healthy adults suggests that semantic knowledge about the use of objects is supported by the left posterior middle temporal cortex rather than the vATL (Johnson-Frey, 2004; Goldenberg & Spatt, 2009; Brandi *et al.*, 2014; Hoeren *et al.*, 2014; Dressing *et al.*, 2016; for a review, see Reynaud *et al.*, 2016). Moreover, in neuroimaging studies, the detection of functional activity in vATL is dependent on a number of technical and methodological factors (Visser *et al.*, 2010). The role that the vATL plays in nonverbal object-action semantics therefore remains unclear.

The overall goal of this study was to address the differences and commonalities in brain activation (specifically in vATL) underlying the verbal and non-verbal semantic retrieval of object-action associations in adults without brain damage. For this purpose, we adapted a classic verb association paradigm to include pantomime production (Petersen *et al.*, 1988, 1989; Thompson-Schill *et al.*, 1997, 1998). Pantomimes are iconic gestures that express meaning through visual similarity (Wilcox, 2004; Emmorey, 2014). In particular, object-oriented pantomimes (such as those for tool-use) are comparable to verbs because both object-oriented pantomimes and verbs are transitive and require retrieval of object-action associations from semantic memory. We used behavioural measurements to assess differences in response time and accuracy between verb and pantomime production (Experiment 1). We further used functional magnetic resonance imaging (fMRI) with sufficient coverage of the anterior temporal lobe (including ventral inferior temporal gyrus and temporal pole) to identify differences in the neural substrates of verb and pantomime production (Experiment 2). In both experiments, we used the same association paradigm to compare verb and pantomime production and additionally compared each condition to verbal

and manual non-semantic baseline responses to control for differences in motor planning associated with articulation and hand movement. Previous studies have suggested that vATL is sensitive to stimulus modality, with left vATL responding more strongly to word and right vATL to picture stimuli (Visser, Jefferies, & Lambon Ralph, 2009; Rice *et al.*, 2015; Hoffman & Lambon Ralph, 2018; for a review, see Gainotti, 2015). Therefore, in both experiments, we tested two groups of participants, using either words or pictures as stimuli.

Behaviourally, we predicted that verb and pantomime production would show a general effect of response selection, *i.e.*, slower response times and lower accuracy for verbs and pantomimes, compared to their respective baseline responses. Given that the task design did not manipulate cognitive load and required participants to retrieve any semantically related action rather than a specific action, we did not expect to find any behavioural differences between verb and pantomime responses or between word and picture stimuli. Neurally, we expected to find evidence for both components of the controlled semantic cognition framework, *i.e.*, semantic representation and control. Verb and pantomime production both require a certain amount of top-down control during semantic retrieval to ensure that responses are task-appropriate. Therefore, we hypothesized that, in contrast to their respective baseline conditions, verb and pantomime production would both engage regions associated with semantic control, such as the inferior frontal junction and gyrus and the pre-supplementary motor area (Noppeney, Phillips, & Price, 2004; Fedorenko, Duncan, & Kanwisher, 2013; Noonan *et al.*, 2013; Davey *et al.*, 2015). We further predicted that verb and pantomime production would differ in their activation of language-specific fronto-temporal regions associated with lexical retrieval (McDermott *et al.*, 2003; Badre *et al.*, 2005; Snyder, Feigenson, & Thompson-Schill, 2007; Price, 2010) and pantomime-specific fronto-parietal areas associated with manual motor planning (Fridman *et al.*, 2006; Niessen, Fink, & Weiss, 2014; Vry *et al.*, 2015). With respect to the vATL, we predicted that verb and

pantomime production as well as word and picture stimuli would dissociate activity in the left vATL from that in the right vATL, such that activation in left vATL would be strongest for verb responses to word stimuli and activation in right vATL would be strongest for pantomime responses to picture stimuli.

Experiment 1: Behaviour

Materials and Methods

Participants

Forty young adults (3 left-handed) with normal or corrected to normal vision took part in the experiment after giving written consent. All participants identified as native speakers of English. The study was approved by the Human Research Ethics Committee of the University of Queensland. Twenty participants each were randomly assigned to one of two experimental groups (see Table 1 for demographic details). The WRD group completed the verb-pantomime task using verbal stimuli, whereas the PIC group completed the verb-pantomime task using picture stimuli (see below). The two groups were matched for age, gender, education, and vocabulary size (independent, two-sided *t*-tests comparing each demographic variable showed no significant differences, all $p > .05$). Vocabulary size was assessed using two multiple-choice vocabulary tests. In the Homonyms test (http://www.kent.ac.uk/careers/tests/homonyms-test.htm), participants were presented with 55 words and phrases (e.g., ‘to assist’) and had to select from one of two possible synonyms that are homophones of each other (e.g., ‘aide’ or ‘aid’). In the Vocabulary test (http://www.kent.ac.uk/careers/tests/WordMeanings.htm), participants were presented with 44 words (e.g., ‘odious’) and had to select from one of three possible synonyms or definitions (e.g., ‘strong smelling’, ‘dislikable’, or ‘Greek god’). Scores on each test are presented as the proportion of correct responses.

(INSERT TABLE 1 HERE)

Verb-Pantomime Production Task

Participants took part in a novel verb and pantomime production task (see Fig. 1A), in which they were cued to respond to a visual stimulus in a specific way. In the paradigm, two independent, binary, categorical variables were manipulated: condition (experimental, control) and response modality (verbal, manual). In experimental trials, participants were cued to produce either a verb or pantomime. In control trials, participants were cued to produce either a stereotyped verbal or manual response in response to a visual stimulus. In experimental trials, stimuli consisted of nouns or pictures referring to manipulable objects (*e.g.*, scissors, hammer, or shovel). In control trials, the stimulus consisted of the symbol string *#%$&@* or a scrambled picture. During experimental trials, participants were instructed to respond by producing verbs or pantomime gestures related to the object referred to by the stimulus (*e.g.*, scissors – /cut/, hammer – /hit/, shovel – /dig/). Control responses consisted of the non-word /gaga/ in the verbal modality or a pinching gesture of the dominant hand in the manual modality. To include both gross and fine finger movements, the control pinching gesture involved lifting the dominant hand, drawing together and releasing the thumb and opposing fingers. Participants were instructed how to respond to the control stimuli and were trained on all response types prior to the experiment with stimuli not used in the main experiment. During practice, participants were told not to emphasize speed but to 'respond whenever you are ready'. It was further emphasized that experimental responses only had to be action words or gestures related to the stimulus, expressing 'what you typically would do with the object', and that there was no right or wrong answer beyond the response modality.

The stimulus set consisted of 48 nouns (WRD group) or 48 pictures (PIC group), representing manipulable objects. Picture stimuli were selected from the Bank of Standardized Stimuli (Brodeur *et al.*, 2010). In order to reduce task-switching demands, stimuli were presented in blocks of four trials and preceded by an instruction indicating one of four response types ('WORD', 'GESTURE', 'GAGA', 'PINCH'). Instructions at the beginning of each block were presented for 3000 msec, followed by a fixation cross for 2000 msec. At the beginning of each trial, the stimulus was presented centrally for 1500 msec, followed by a fixation cross for 2500 msec. Each stimulus was presented once for each of the verb and pantomime experimental conditions. For each participant, 50% of stimuli were randomly selected and presented to the participant for the first time in the verb condition, while the remaining 50% were presented for the first time in the pantomime condition. Twelve blocks of four trials were presented per condition in a randomized order for a total of 192 trials. After half of the blocks, participants were offered a short break.

(INSERT FIGURE 1 HERE)

Response Recording and Analysis

Stimuli were presented and responses recorded using PsychoPy software (v1.84.2; http://www.psychopy.org/) running on a 2013 Apple Macbook Pro. Response times were measured acoustically. Auditory signals of pantomime onset were generated using a sound-action-monitoring (SAM) box developed at the Centre for Advanced Imaging. The SAM box consists of a piezo speaker and response pad connected to an Arduino microcontroller board (https://www.arduino.cc/). The Arduino microcontroller was programmed to emit a 3.3 kHz sine wave upon response pad press (duration = 50 msec) and upon response pad release (duration = 200 msec). The SAM box allows the recording of the onset and offset of each

gesture via a microphone. During the entire experiment, participants rested their dominant hand on the SAM box, unless they produced gesture responses.

Auditory responses for verbs and pantomimes were recorded for 4 sec from stimulus onset. The experimenter monitored each participant's responses and false responses or response omissions were noted as errors and excluded from further analysis. Correct verbal responses were transcribed. Response times were derived from audio recordings using Praat software (v6.0.24; http://www.fon.hum.uva.nl/praat/) and custom scripts. First, a TextGrid file containing sound onsets and offsets was created automatically from each audio file using Praat with the following parameters: 100 Hz minimum pitch, 10 msec time step, silence threshold -25 dB, minimum silent and sounding interval durations of 100 msec. Then, each annotation file was manually checked against the spectrogram, intensity, formants, and glottal pulses, and incorrect automatic annotations were manually corrected. Finally, the onset of each response was extracted from the TextGrid files and statistically analyzed using R (https://cran.r-project.org/).

Results

A 2x2x2 analysis of variance of response times with between-subjects factor group (WRD, PIC) and within-subjects factors condition (test, control) and response modality (verbal, manual) revealed significant main effects for factors condition ($F(1,1) = 1019.9$, $p < .001$), and response modality ($F(1,1) = 106.4$, $p < .001$), as well as a significant interaction between condition and response modality ($F(1,1) = 92.4$, $p < .001$). The results did not show any group effects (all $p > .05$; for a summary of results, see Fig. 2). Paired *t*-tests, comparing response times between response modalities for the baseline control conditions for each group did not show any significant differences (all $p > .05$ uncorrected). Together, these

results demonstrate that response times are significantly larger for verb responses compared to pantomime responses in the test but not the control condition .

A 2x2x2 analysis of variance of error percentages with between-subjects factor group (WRD, PIC) and within-subjects factors condition (test, control) and response modality (verbal, manual) revealed significant main effects for factors condition ($F(1,1) = 48.9$, $p < .001$), and response modality ($F(1,1) = 15.5$, $p < .001$), as well as a significant interaction between condition and response modality ($F(1,1) = 15.1$, $p < .001$). The results did not show any group effects (all $p > .05$; for a summary of results, see Fig. 2). Paired *t*-tests, comparing error percentages between response modalities for the baseline control conditions for each group did not show any significant differences (all $p > .05$ uncorrected). Together, these results demonstrate that error percentages are significantly higher for verb responses compared to pantomime responses in the test but not the control condition.

In addition, correlation tests between response times and accuracy and education, age, and vocabulary size revealed that education was negatively correlated with error rates during verb production ($r = -.5$, $t(38) = 3.5$, $p < .005$ Bonferroni corrected). That is, participants with more education made fewer errors when production verbs than participants with less education.

(INSERT FIGURE 2 HERE)

Experiment 2: Functional Neuroimaging

Materials and Methods

Participants

Forty-four right-handed young adults with normal or corrected to normal vision took part in the experiment after giving written consent (for demographic details, please see Table

1). The study was approved by the Human Research Ethics Committee of the University of Queensland. All participants identified as native speakers of English and were screened for neuropsychological and neurological disorders, as well as for psychotropic medication and substance use. Twenty-two participants each were randomly assigned to one of two experimental groups. The WRD group completed the Verb-Pantomime Production task, using verbal stimuli, whereas the PIC group completed the Verb-Pantomime Production task, using picture stimuli. The two groups were matched for age, gender, education, and vocabulary size (independent, two-sided *t*-tests comparing each demographic variable showed no significant differences, all $p > .05$). Vocabulary size was assessed using the Homonyms and Vocabulary tests described in Experiment 1 above.

Procedure

Participants took part in the Verb-Pantomime Production task described above, which was modified for fMRI to optimize signal acquisition during response selection (see Fig. 1B). In contrast to Experiment 1, a response cue was added to the paradigm to reduce neural activity associated with overt movement and to avoid differences in response latency between conditions and across individuals (Fridman et al., 2006). Participants were instructed to produce their responses only upon seeing the response cue, which consisted of a green circle presented centrally 3500 msec after stimulus onset for 1000 msec. In addition, the inter-trial interval was jittered and ranged from 2000 to 4250 msec, resulting in an average trial duration of 7750 msec. During each of six imaging runs, 12 blocks of four trials were presented per condition and the order of the blocks was randomized. Stimuli were presented using Presentation software (Neurobehavioral Systems Inc., Berkeley, CA, USA). The experimenters monitored each participant's responses visually and aurally through a FOMRI-III MR-compatible noise-cancelling microphone (Optoacoustics Ltd., Moshav Mazor, Israel) attached to the participant's head coil to ensure compliance with task instruction. Trials, in

which participants produced a wrong response were excluded from the analysis. As in the behavioural Verb-Pantomime Production task, participants were instructed how to perform the stereotyped control responses and were trained on all conditions, prior to the experiment, with stimuli not used in the experiment. Participants were further made aware of the effects of head movements on data quality and were instructed to minimize their movements during gesture responses, *i.e.*, to only move their forearm and hand.

MRI Acquisition Parameters

Images were acquired with a Siemens Magnetom Trio 3T scanner and a 32-channel head coil at the Centre for Advanced Imaging at the University of Queensland. For each participant, a T1-weighted volumetric anatomical MRI was acquired with the following parameters: 176 slices sagittal acquisition MP2-RAGE; 1 mm^3 isotropic volume; repetition time (TR) = 4000 msec; echo time (TE) = 2.89 msec; flip angle = 6°; FOV = 256 mm, GRAPPA acceleration factor = 3. Functional images were acquired using a T2*-weighted echo-planar image sequence with the following parameters: 45 slices; 2.5 mm^3 isotropic volume (10% distance between slices); TR = 3000 msec; TE = 30 msec; FOV = 190 mm; flip angle = 90°.

Multivariate Whole-Brain Analysis

Brain activation was assessed using the blood oxygenation level dependent (BOLD) effect (Ogawa *et al.*, 1990). For functional analysis, T2*-weighted images were preprocessed with Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm). Images were realigned to the mean image for head-motion correction and then spatially normalized into standard stereotaxic space with a voxel size of 2 mm^3 (Montreal Neurological Institute template) using segmented white and gray matter T1 maps. Head movement and rotation in the three dimensions did not exceed 2 mm or 2º, respectively, and

no dataset had to be excluded from analysis. Finally, the functional images were spatially smoothed with an 8-mm full width half maximum Gaussian kernel.

Following preprocessing, whole-brain fMRI data from both groups were analyzed together using Partial Least Squares (PLS; https://www.rotman-baycrest.on.ca/index.php?section=84). PLS is a model-free, multivariate analysis tool similar to principal component analysis (McIntosh, Chau, & Protzner, 2004). PLS is based on the assumption that the neural activity underlying cognitive processes is best analyzed as the coordinated activity of groups of voxels rather than the independent activity of any single voxel (McIntosh & Lobaugh, 2004; Krishnan *et al.*, 2011). In brief, PLS mean-centers and then decomposes the covariance matrix between brain activity and the experimental design for all participants in a single analytic step using singular value decomposition (SVD). SVD results in separate, mutually orthogonal latent variables (LVs), which describe patterns of brain activity related to the experimental design (McIntosh, Chau, & Protzner, 2004; Krishnan *et al.*, 2011). SVD maximizes covariance in the partial least squares sense and generates a weight for each voxel, which designates its degree of covariance with the whole brain activity pattern. PLS then assesses the statistical significance of each LV using permutation testing with 500 permutations (McIntosh *et al.*, 1996) and the reliability of the brain activity patterns for each voxel by using a bootstrapping procedure with 100 bootstraps, resulting in an estimate of the standard error, which is used to calculate the bootstrap ratio (Efron & Tibshirani, 1985). Peak voxels with a minimum bootstrap ratio of 3 are considered to be reliable (Sampson *et al.*, 1989). In PLS, computation of LVs and corresponding brain images is conducted in a single analytic step across all voxels and participants; therefore, no correction for multiple comparisons is required. Finally, a brain score, indicating how strongly each resulting pattern is expressed in each individual participant, is calculated by multiplying each individual data set with the whole-brain activation loadings.

It is worth noting that this study differed from previous studies on vATL activation in the use of partial least squares (PLS) for the whole-brain analysis. In contrast to more commonly used generalized linear models, PLS not only considers the temporal relationship between task design and fMRI data but also the spatial relationship between activated voxels. As a spatio-temporal analysis method, PLS is based on the joint variance of individual voxels and is, thus, more sensitive to the covariance of brain activity. As such, our results are not based on contrasts that show regions that are more or less engaged during one condition than during another (*i.e.*, our results do not follow the logic of the subtraction method). Rather, our results show changes in brain activity related to task manipulations and uncover the brain's responses to differences between conditions.

Results

Whole-brain fMRI analysis revealed three significant latent variables (LVs; all $p < .005$). The first LV accounted for 53% of the covariance within the data and revealed an effect of response modality, *i.e.*, it differentiated brain activation patterns related to verb production and its associated baseline responses from pantomime production and its respective baseline responses across both groups. The verb-related brain activity pattern included bilateral ventral anterior temporal lobe, lingual gyrus, fusiform gyrus, posterior middle temporal gyrus, secondary somatosensory cortex (posterior operculum), mid-cingulate gyrus, central sulcus, pre- and post-central gyrus, supplementary motor area, paracentral lobule, inferior and superior parietal cortex, caudate nucleus, thalamus, anterior putamen, left orbital inferior frontal gyrus (BA47), inferior frontal junction, anterior insula, and premotor cortex, as well as right hippocampus and cerebellum. Non-overlapping 95% confidence intervals demonstrate that this pattern was significantly more strongly related to

verb trials than its respective baseline responses (see Fig. 3A). The pantomime-related brain activity pattern included bilateral fusiform gyrus, posterior middle temporal gyrus, posterior operculum, opercular inferior frontal gyrus (BA44), superior occipital gyrus, inferior and superior parietal lobe, postcentral gyrus, precuneus, posterior cingulate cortex, ventral striatum, cerebellum, left mid-cingulate gyrus and supplementary motor area. 95% confidence intervals demonstrate that there was no significant difference in activation between pantomime production and its respective baseline responses (see Fig. 3B).

(INSERT FIGURE 3 HERE)

The second LV accounted for 18% of the covariance within the data and demonstrated an effect of task condition, *i.e.*, it differentiated brain activation patterns related to verb and pantomime production from their respective baseline responses across both groups. The brain activation pattern related to verb and pantomime production included left inferior frontal gyrus (BA44, 45), anterior insula, inferior frontal junction, pre-SMA, premotor cortex, posterior inferior temporal gyrus, inferior parietal sulcus, bilateral fusiform gyrus, anterior striatum, caudate nucleus, thalamus, and right cerebellum. 95% confidence intervals demonstrate that there was no significant difference in activation between verb and pantomime production (see Fig. 4A). The brain activation pattern related to baseline responses included right secondary somatosensory cortex (posterior operculum), temporal-parietal junction, posterior cingulate cortex, and middle temporal gyrus. 95% confidence intervals demonstrate that there was no significant difference in activation between verbal and manual baseline responses (see Fig. 4B).

(INSERT FIGURE 4 HERE)

The third LV accounted for 11% of the covariance within the data and showed an effect of stimulus modality or group, *i.e.*, it differentiated brain activation patterns related to the WRD group from the PIC group. The brain activity pattern related to picture stimuli included bilateral lingual gyrus, middle occipital gyrus, fusiform gyrus, parahippocampal gyrus, precuneus, superior parietal lobule, and left inferior parietal sulcus. Non-overlapping 95% confidence intervals demonstrate that this pattern was more significantly strongly related to verb than to pantomime trials (see Fig. 5A). The brain activity pattern related to word stimuli included left orbital inferior frontal gyrus (BA47), bilateral ventromedial prefrontal cortex, and right parahippocampal gyrus. Non-overlapping 95% confidence intervals show that this pattern was significantly more strongly related to verb than to pantomime production (see Fig. 5B).

(INSERT FIGURE 5 HERE)

Post-Hoc Analysis of vATL Responses

Based on the results of the whole-brain analysis, which showed significant engagement of vATL for verb production, and previous studies, which reported effects of stimulus modality on vATL activation (Rice *et al.*, 2015; Hoffman & Lambon Ralph, 2018), we decided to investigate whether vATL would show hemispheric differences in response to word or picture stimuli along its rostro-caudal gradient. We extracted the average change in BOLD signal in response to stimuli for verb and verbal baseline control trials from nine clusters within the left and right vATL, which were evenly spaced 6 mm apart along the y-axis (from y = 18 to y = -30). The clusters were defined as voxels adjoining the peak voxel in

the respective coronal slice that was located ventrally to the anterior temporal white matter (see Fig. 6 & Table 2).

A 2x2x2x9 ANOVA with between-subjects factor group (WRD, PIC) and within-subjects factors condition (verb test, verb control), hemisphere (left, right), and location (nine clusters) revealed a significant main effect of location ($F(1,8) = 20.2$, $p < .001$, Greenhouse Geisser corrected), a significant interaction between hemisphere and location ($F(1,8) = 3.7$, $p < .05$, Greenhouse Geisser corrected), and a significant interaction between group, condition, and hemisphere ($F(1,1) = 5.9$, $p < .001$). Nine one-way ANOVAs clarified the interaction between hemisphere and location by showing that BOLD signal change was significantly stronger in the left than the right hemisphere at y = 6 ($F(1,1) = 13.6$, $p < .01$, Bonferroni corrected) and at y = -18 ($F(1,1) = 10.3$, $p < .05$, Bonferroni corrected). Following up on the three-way interaction, two 2x2 ANOVAs with within-subjects factors condition and hemisphere revealed an interaction in the WRD group, which approached significance ($F(1,1) = 3.5$, $p = 0.08$, uncorrected) and indicated potentially stronger signal changes in the right vATL for verb responses. Together, these results do not provide evidence for hemispheric differences in response to word or picture stimuli along the vATL's rostro-caudal gradient.

(INSERT FIGURE 6 HERE)

Discussion

The aim of this study was to investigate the functional role of vATL in the retrieval of object-action associations for verb and pantomime production. The main findings demonstrate that verb, but not pantomime, production engages vATL bilaterally, and that the retrieval of object-action associations is more slower and more error-prone for verb compared

to pantomime production. Importantly, our results demonstrate that vATL activation is not sensitive to stimulus modality and that vATL is also engaged during the production of stereotyped verbal control responses to meaningless stimuli, which do not involve object-action associations. Our results further show that verb and pantomime production share neural activity generally associated with domain-general semantic control (Noppeney, Phillips, & Price, 2004; Fedorenko, Duncan, & Kanwisher, 2013; Noonan *et al.*, 2013; Davey *et al.*, 2016).

In line with our expectations, the results show differential activation for verb and pantomime responses. However, in contrast to our predictions, activity in vATL, including the temporal pole and the ventrolateral aspects of the anterior inferior temporal gyrus, was only observed for verb but not pantomime production. Interestingly, this activity was associated with the production of verbs, which required the retrieval of object-action associations in response to word or picture stimuli, as well as for the production of a meaningless verbal control response to a non-semantic stimulus. Post-hoc comparisons further demonstrated that BOLD signal changes were strongest in the region of the proposed transmodal hub for both hemispheres (Binney *et al.*, 2010; Shimotake *et al.*, 2015; Chen *et al.*, 2016; Murphy *et al.*, 2017).

Our finding that vATL is involved in verb production aligns with clinical evidence that progressive fluent aphasia, *i.e.*, anomia with preserved syntax and phonology, constitutes the most prominent symptom of semantic dementia (Snowden, Goulding, & Neary, 1989; Hodges *et al.*, 1992). However, the absence of any activity in vATL during pantomime production suggests that the impairment on nonverbal object-use tasks in semantic dementia might not be the result of pathological changes in the vATL. One possible source of this impairment might instead be pathological changes in more posterior temporal regions, which have previously been shown to support object-action representations (Johnson-Frey, 2004;

Brandi *et al.*, 2014). In fact, a morphometric study showed that in semantic dementia, temporal lobe atrophy is likely to extend to the posterior middle temporal gyrus (Mummery *et al.*, 2000). Similarly, a study of a semantic dementia patient with severe anomia for nouns demonstrates that verbal and nonverbal object-action associations are intact when temporal lobe atrophy does not extend to posterior regions (Breedin, Saffran, & Coslett, 1994; Buxbaum, Schwartz, & Carew, 1997). Our results show that the posterior middle temporal gyrus is engaged during verb as well as pantomime production, but not their respective baseline controls as part of a larger pattern associated with semantic control (Whitney *et al.*, 2010; Noonan *et al.*, 2013). Importantly, this result suggests that the reduction in semantic control rather than the degradation of semantic representations might be responsible for the impaired performance of nonverbal object-action association tasks previously observed in semantic dementia patients. This interpretation is further supported by evidence from comparisons of semantic dementia (SD) with other patient groups with anterior temporal lobe damage and semantic deficits, such as temporal lobe epilepsy (TLE) or herpes simplex virus encephalitis (HSVE) patients. In contrast to SD patients, TLE patients generally show deficits in language production but not comprehension before and after unilateral surgical resection of the anterior temporal lobe (Giovagnoli *et al.*, 2005; Lambon-Ralph *et al.*, 2012). This evidence suggests that more complex semantic deficits, such as impaired nonverbal object-action associations, are the result of more widespread atrophy and cannot be localized to the vATL alone. Similarly, in contrast to SD patients, HSVE patients commonly show category-specific semantic deficits and their atrophy is more restricted to the anterior medial rather than posterior lateral portions of the temporal lobe, which also points to a causal relationship between domain-general semantic impairments and temporal lobe atrophy beyond vATL (Noppeney *et al.*, 2007; Frisch *et al.*, 2015).

Contrary to findings in some previous neuroimaging studies (Rice *et al.*, 2015; Hoffman & Lambon Ralph, 2018), our results did not show any effect of stimulus modality on vATL activation. Instead, our data show that activity in vATL is strongly modulated by response modality. This discrepancy in findings can be attributed to methodological differences. Importantly, we ensured coverage of the ventral ATL, whereas the results of the meta-analysis by Rice *et al.* (2015) were restricted to dorsal regions of ATL, and recent evidence suggests that dorsal ATL rather than vATL is sensitive to stimulus modality (Murphy *et al.*, 2017). In contrast to both previous studies, our analysis was statistically conservative and does not report results based on uncorrected *p*-values (Rice *et al.*, 2015) or collapsed experimental conditions (Hoffman & Lambon Ralph, 2018), which may have led previous studies to over-estimate the effects of stimulus modality on vATL activation. Instead, our data suggest that vATL is highly sensitive to tasks involving verbal responses.

A surprising result of our study is that vATL is also engaged bilaterally during the production of a stereotyped verbal control response to a scrambled picture or a meaningless symbol string. One interpretation of this finding is that the stimulus acquired meaning by becoming associated with the particular response. However, activation to the same stimulus did not occur with production of stereotyped pantomime control responses, suggesting that vATL is particularly sensitive to responses in the verbal modality. Taken together, these findings question the previously hypothesized function of vATL as a transmodal semantic hub and instead suggest that vATL might be functionally specialized for language.

This interpretation is in line with the predominant symptom of anomia in semantic dementia patients. However, this interpretation is at odds with findings in non-brain damaged adults that show that vATL is engaged in semantic judgements for verbal and non-verbal stimuli (Visser & Lambon Ralph, 2011; Hoffman & Lambon Ralph, 2018). One explanation for this discrepancy might simply be that participants covertly verbalised their responses or

the stimuli during semantic judgement. An alternative explanation for this discrepancy is that vATL is engaged in retrieving arbitrary symbolic associations rather than language. Our findings somewhat support this interpretations since our paradigm compared verbs, which do involve symbolic associations, with pantomimes, which instead involve iconic associations. A third possible explanation for this discrepancy is that vATL is crucial for the formation, maintenance, and retrieval of systematic rather than incidental conceptual associations (Lambon Ralph *et al.*, 2010; Lambon Ralph, 2014) and that semantic judgements rely on this mental lexicon. This view is supported by our findings because verbs and pantomimes differ profoundly in their degree of systematic organization. Verbs are organized in a lexical system of oppositions, equivalencies, and collocations with other words and require lexical retrieval, whereas pantomimes are produced spontaneously from motor imagery. Therefore, vATL might support the retrieval of systematic conceptual relations, which underlie language as well as semantic judgements.

This interpretation is further supported by our observation that orbital ventrolateral prefrontal cortex (vlPFC; BA47) was engaged in addition to the vATL during verb production. Orbital vlPFC has been found in several studies to be involved in lexical-semantic retrieval (Poldrack *et al.*, 1999; Müller, Kleinhans, & Courchesne, 2003; Badre *et al.*, 2005; Danelli *et al.*, 2015), and semantic priming experiments show that orbital vlPFC is engaged in strategic semantic retrieval (Gold *et al.*, 2006). Orbital vlPFC and vATL are directly connected through the extreme capsule, constituting the ventral language pathway (Saur *et al.*, 2008). Given that lexical selection is required for language but not gesture production, the observed activation of BA47 and vATL during verb production is likely to relate to lexical-semantic retrieval. This view fits the argument that any systematic conceptual organisation (such as a mental lexicon) requires abstract semantic representations, which in humans might be subserved by the vATL (Lambon Ralph *et al.*, 2010; Lambon

Ralph, 2014). This interpretation is further supported by our behavioural finding that verb production is slower and more error-prone than pantomime production but that control responses are comparable between the two modalities. Any higher-order, systematic conceptual organisation enables new sources of error and requires additional control compared to a simpler, non-systematic system. Therefore, our behavioural and neuroimaging results together indicate that the fast and appropriate production of verbs requires the efficient interaction of vATL and orbital vlPFC to retrieve semantic associations from the mental lexicon.

In addition to frontal-temporal regions, we showed that verb production engages bilateral somatosensory (postcentral gyrus, anterior insula, posterior operculum) and motor areas (SMA, premotor and primary motor cortex), as well as subcortical regions (pallidum, thalamus) more strongly than during baseline responses. These regions have all previously been linked to phonological-articulatory processes, which prepare the motor system for overt speech and thus likely reflect lexical-phonological retrieval (Ackermann & Riecker, 2004; Riecker *et al.*, 2005; Bohland & Guenther, 2006; Brown *et al.*, 2009).

In contrast to verbs, pantomime production engaged large portions of parietal cortex and opercular vlPFC (BA44) to a similar extent as its manual baseline response. The neural activation underlying pantomimes has previously been investigated in the context of apraxia. In patients with apraxia, impaired pantomimes of tool use are associated with lesions in left inferior frontal gyrus and inferior parietal cortex (Goldenberg *et al.*, 2007; Niessen, Fink, & Weiss, 2014). Pantomimes of tool use engage both semantic-conceptual and practical-motor processing, with a distinct ventral-dorsal system for object use and a dorsal-dorsal system for object grasping being previously proposed (Johnson-Frey, 2004; Buxbaum & Kalénine, 2010; Binkofski & Buxbaum, 2012; Hoeren *et al.*, 2014). According to this model, pantomimes of tool use rely on two different processing streams, which converge on inferior

frontal gyrus, particularly pars opercularis (BA44), for action selection (Goldenberg *et al.*, 2007; Dressing *et al.*, 2016). Our neuroimaging results support this view by showing that pantomime production and its baseline control are associated with activity in opercular vlPFC, inferior parietal, and superior parietal cortices, which likely reflects the engagement of the ventral-dorsal, object-use and dorsal-dorsal, object-grasping pathways during motor planning for pantomime production.

The shared activity pattern related to verb and pantomime production – but not their respective baseline responses – comprises vlPFC, including opercular and triangular inferior frontal gyri (BA44, 45), inferior frontal junction, premotor cortex, anterior insula, pre-SMA, posterior middle temporal gyrus, and inferior parietal sulcus. Previous studies have shown that these regions are engaged during cognitive control over conceptual-semantic response selection (Noppeney, Phillips, & Price, 2004; Cole & Schneider, 2007; Whitney *et al.*, 2010; Fedorenko, Duncan, & Kanwisher, 2012, 2013; Davey *et al.*, 2016; Hallam *et al.*, 2016) and controlled language switching in bilinguals (Abutalebi & Green, 2007; Luk *et al.*, 2011; Green & Abutalebi, 2013). Patient studies have further demonstrated that damage to these regions results in deregulated verbal and nonverbal semantic cognition (Jefferies & Lambon-Ralph, 2006; Corbett *et al.*, 2009; Corbett, Jefferies, & Ralph, 2011; Gardner *et al.*, 2012).

Beyond cortical regions, the shared pattern also included extensive subcortical activation in the thalamus, caudate nucleus, and anterior pallidum during verb and pantomime production but not their respective baseline responses. It has previously been suggested that cognitive control over conceptual-semantic response selection is associated with an associative frontal – basal ganglia – thalamocortical loop (Crosson, 2013; Hart *et al.*, 2013; Dick, Bernal, & Tremblay, 2014). Patient studies demonstrate the contribution of this associative loop to a number of different language-related processes involving semantic control. Lesion studies have shown that the basal ganglia are engaged in lexical and syntactic

processing (Fabbro, Clarici, & Bava, 1996; Copland *et al.*, 2000a, 2000b, 2000c; Friederici *et al.*, 2003; Longworth *et al.*, 2005). Aphasic patients with dominant thalamic lesions demonstrate semantic paraphasias (Crosson, 1984, 2013; Raymer *et al.*, 1997) and aphasic patients with bilateral thalamic lesions show a specific impairment for semantic processing of verbs (De Witte *et al.*, 2005). Neuroimaging studies of non-brain damaged participants have further found specific activation of the basal ganglia and thalamus for syntactic sequencing (Chan, Ryan, & Bever, 2013), lexical decision (Tiedt *et al.*, 2017), word generation (Crosson *et al.*, 2003), speech production (Eickhoff *et al.*, 2009), language switching (Luk *et al.*, 2011), and language selection (Abutalebi *et al.*, 2008). In line with our hypothesis, these results suggest that verb and pantomime production activate the same cortical-subcortical cognitive or semantic control network during response selection. This increase in semantic control is reflected in the behavioural results of experiment 1, which show that the production of verbs and pantomimes is slower and more error-prone than to the production of stereotyped control responses that do not require semantic control.

The findings of this study have implications for theories of gesture production. Specifically, the findings might help us better understand previous findings that gestures are mostly elicited during cognitively demanding tasks (Kita, Alibali, & Chu, 2017), when cognitive resources are low (Marstaller & Burianová, 2013; Gillespie *et al.*, 2014; Pouw *et al.*, 2016), or when other processes are ineffective, *e.g.*, during word finding difficulties (Krauss, Chen, & Gottesman, 2001). It has been suggested that the lower control demands of gestures free up cognitive resources and thereby lighten the cognitive load (Goldin-Meadow *et al.*, 2001; Cook, Yip, & Goldin-Meadow, 2012). However, rather than lightening the load, gestures might enable communication or cognitive planning to proceed when verbal working memory, which relies heavily on language, is overloaded. Due to the lack of lexical retrieval, gestures have a smaller cognitive load. Yet, gestures are able to fulfil some of the core

functions of language by engaging the same executive control processes for conceptual-semantic response selection and by producing meaningful, context-sensitive communicative behaviour. As such, the use of gestures might constitute a contingency mechanism, which is consistently available but is only employed once the dominant strategy, *i.e.*, language, is delayed, fails, or – in the case of young children – is not yet fully developed.

In sum, our findings have implications for the controlled semantic cognition framework (Patterson *et al.*, 2007; Lambon Ralph *et al.*, 2017). Our findings do not support the hypothesis of a transmodal, domain-general hub in the vATL. However, our findings provide support for a neurocognitive system for controlled semantic retrieval during verb and pantomime production. Based on our findings, we suggest that the controlled semantic cognition framework is amended to better reflect the influence of language on semantic cognition and classify vATL as heavily shaped by language. Additional amendments depend on future studies, which should further investigate the role of vATL and other temporal lobe structures in supporting non-verbal object-action associations.

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Figure Captions:

Figure 1 – Verb Pantomime Task: Two versions of the task optimized for behavioural (A) and neuroimaging (B) experiments. Following a block instruction, participants respond to four stimuli (words or pictures) by producing a meaningful (test) or baseline (control) response in the verbal or manual domain. In the neuroimaging version (B), participants withhold their response until they are presented with a green dot to reduce noise stemming from overt motor activity.

Figure 2 – Behavioural Results: The bar plots show mean response times (Speed, top) and error percentages (Accuracy, bottom) plus standard errors of the mean for responses to word stimuli (WRD) and picture stimuli (PIC) for all four conditions (Panto – Pantomime; Con – Control).

Figure 3 – Effect of Response Modality Indexing Language-Specific Activation: Whole-brain activation plots show increased activation for A) verb (left) and B) pantomime (right) trials. Bar plots show brain scores (plus 95% CIs) for each condition and group, which indicate how strongly the brain activation pattern below is represented in each group and each condition (Panto – Pantomime; Con – Control; WRD – word stimuli group; PIC – picture stimuli group).

Figure 4 – Effect of Task Condition Indexing Domain-General Activation: Whole-brain activation plots show increased activation for A) test (left) and B) control (right) trials. Bar plots show brain scores (plus 95% CIs) for each condition and group, which indicate how strongly the brain activation pattern below is represented in each group and each condition

(Panto – Pantomime; Con – Control; WRD – word stimuli group; PIC – picture stimuli group).

Figure 5 – Effect of Stimulus Modality/Group: Whole-brain activation plots show increased activation for participants completing the task using A) picture (left) or B) word stimuli (right). Bar plots show brain scores (plus 95% CIs) for each condition, which indicate how strongly the brain activation pattern below is represented by each group (Panto – Pantomime; Con – Control; WRD – word stimuli group; PIC – picture stimuli group).

Figure 6 – vATL Activations during Verb Production: The figure shows BOLD signal changes in left and right vATL along the rostro-caudal axis during verb production from word (WRD) and picture (PIC) stimuli.

Group	N	Age	Edu	Hom	Voc
Experiment 1: Behaviour					
WRD	20	25.0 (4.09)	16.7 (2.08)	0.9 (0.05)	0.7 (0.13)
PIC	20	25.3 (4.21)	17.1 (2.49)	0.9 (0.05)	0.7 (0.11)
Experiment 2: Functional Neuroimaging					
WRD	22	25.0 (3.34)	16.1 (2.55)	0.9 (0.06)	0.7 (0.14)
PIC	22	25.8 (6.26)	16.4 (2.97)	0.9 (0.05)	0.7 (0.09)

Table 1 – Participant information for Experiments 1 & 2: Table shows means (and standard deviations) for each measure. WRD – word stimuli group; PIC – picture stimuli group; N – number of participants (50% females in each group); Age – age (years); Edu – formal education (years); Hom – Homonyms test result (proportion correct); Voc – Vocabulary test result (proportion correct).

LEFT vATL

x	*y*	*z*	*# voxels*	*Anatomical Region*
-40	18	-40	21	Temporal Pole
-40	12	-44	23	Temporal Pole
-46	6	-46	20	Temporal Pole / Inferior Temporal Gyus
-50	0	-42	27	Inferior Temporal Gyrus / Temporal Pole
-46	-6	-42	27	Inferior Temporal Gyrus
-56	-12	-38	26	Inferior Temporal Gyrus
-58	-18	-34	26	Inferior Temporal Gyrus
-52	-24	-28	27	Inferior Temporal Gyrus
-50	-30	-28	27	Inferior Temporal Gyrus

RIGHT vATL

x	*y*	*z*	*# voxels*	*Anatomical Region*
42	18	-40	22	Temporal Pole
38	12	-44	27	Temporal Pole
44	6	-40	27	Temporal Pole / Inferior Temporal Gyrus
50	0	-42	26	Inferior Temporal Gyrus
44	-6	-42	27	Inferior Temporal Gyrus
48	-12	-42	27	Inferior Temporal Gyrus
42	-18	-32	27	Fusiform Gyrus / Inferior Temporal Gyrus
64	-24	-28	27	Inferior Temporal Gyrus
50	-30	-28	26	Inferior Temporal Gyrus

Table 2 – Coordinates of vATL Regions of Interest: Table shows coordinates of peak voxel in MNI space, size of ROI centered on peak voxel in voxels, as well as the anatomical location of the ROI following the Harvard Oxford Cortical Atlas.